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Title: **Excess copper and *ceruloplasmin* biosynthesis in long-term cultured hepatocytes from Long-Evans Cinnamon (LEC) rats, a model of *Wilson* disease.**

Author(s): Nakamura K; Endo F; Ueno T; Awata H; Tanoue A; Matsuda I

Author's Address: Department of Pediatrics, Kumamoto University School of Medicine.

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Abstract: Immortalized hepatic cell lines obtained from laboratory animals or patients with defects in copper metabolism in the liver provide new approaches to examine related metabolism and toxicity. We established a series of hepatic cell lines from the liver of Long-Evans Cinnamon (LEC) rats, using recombinant adenovirus which expresses SV40 large T. Cells from the LEC rats were cultured and accumulated larger amounts of copper than did control cells, when the concentrations of copper in the culture medium exceeded 5 microM. The secretion of ***ceruloplasmin*** (CP) from the cultured cells was not reduced in hepatocytes from LEC cells, as compared with the control cells. As accumulation of copper did not affect CP secretion, CP production was not likely to be affected by the accumulation of copper in LEC rat hepatocytes. The production of holo-CP was further investigated by transfection of human CP cDNA and detection of human holo-CP by immunological procedures and use of a monoclonal ***antibody*** (mAb CP60) which recognizes human holo-CP but not human apo-CP and rat CP. Hepatocytes from the LEC rats processed and secreted holo-CP into the medium, even with excess copper present in the medium. These observations suggest that the genetic defect in LEC rats did not alter biosynthetic and secretory pathways of CP and that the intracellular copper concentration did not regulate the synthesis and processing of CP in the cultured hepatocytes. Low ***ceruloplasmin*** levels are observed in most, but not all, patients with ***Wilson*** disease, as well as in LEC rats. Our results do suggest that the copper transporting ATPase encoded in the ***Wilson*** disease gene is not a integral part of the biochemical mechanism of copper incorporation into apoprotein. The cell lines and immunological procedures we used are expected to add to information on biologically important process related to copper metabolism and to CP biosynthesis.

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